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Thesis abstract

Investigation of type I interferon and immune signalling in breast and ovarian cancer

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The type I interferons (IFN) are a family of innate immune cytokines known to play vital roles in host defence. The direct and indirect anti-tumour effects of these cytokines have led to considerable investigation into their role in cancer pathogenesis and their use as potential anti-cancer therapeutics. Despite this, the clinical use and benefit of type I IFN therapy has so far been limited to a select number of cancers such as melanoma and haematological malignancies. Notably, the success of IFN treatment has varied widely among patients and cancer types including many solid tumours where IFN therapy has exhibited poor efficacy and is largely restricted by dose-limited toxicity. The greater potential of these cytokines as anti-cancer agents has yet to be realised and to this end, there is a clear need to further understand the complexities of type I IFN signalling in cancer development and progression.

New insights into the molecular pathways underlying cancer progression reveal further evidence of dysregulated type I IFN signalling. Specifically, the presence of constitutive IFN signalling in mammary epithelium as well as primary breast tumours has been shown to be suppressed in bone metastases. Here, suppression of constitutive IFN was characterised as a critical mechanism of immune evasion facilitating successful breast cancer metastasis, although the processes underlying this metastatic pathway remained unclear. Meanwhile, a distinct type I IFN, IFNε, has been characterised as constitutively expressed in epithelial cells of the female reproductive tract (FRT), with previously unexplored anti-tumour properties, potentially critical in restricting FRT malignancies such as ovarian cancer. The significance of continuous IFN activity in the pathogenesis and additionally, the metastasis of these tumours remain to be characterised. The central aims of this thesis were to use these two models of cancer, breast and ovarian, to firstly: determine whether characterising IFN signatures in peripheral blood could provide further insight into cancer metastasis or derive novel biomarkers for patient stratification; and secondly: to investigate the previously unknown anti-tumour potential of a distinctly constitutive type I IFN, IFNε. In breast cancer, this work investigated local, systemic and distant signatures to characterise the processes underlying metastasis and map a continuum of disease progression from normal tissue to metastases. Blood transcriptomics revealed a strong enrichment of platelet activity, T cell suppression and broad IFN involvement, which were further investigated by multiplexed staining of tumour tissue to correlate key immune-tumour cell interactions with

metastatic potential. In ovarian cancer, this work demonstrated patterns of constitutive IFNε expression never before characterized – in the tissue of origin of high grade serous ovarian carcinomas (HGSC). In addition, this study demonstrated the first evidence of the loss of constitutive IFNε in human HGSC development and has also revealed IFNε to be an effective anti-metastatic therapy in mouse models of orthotopic and disseminated ovarian cancer, through both intrinsic and extrinsic pathways of tumour suppression providing the basis for the use of IFNε as an anti-cancer therapy.

Thus, this thesis contributes to the knowledge of constitutive type I IFN in tumorigenesis and tumour progression and demonstrates the potential use of endogenous IFN signalling and immune signatures for patient stratification in cancer progression as well as targeted anti-metastatic exogenous IFN therapy.

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URL: https://figshare.com/articles/Investigation_of_Type_I_Interferon_and_Immune_Signalling_in_Breast_and_Ovarian_Cancer/7122320